REMARKS

Claims 177 and 210-214 presently appear in this case. No claims have been allowed. The official action of September 19, 2006, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that either inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid. The genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that either recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The human monoclonal antibody must be one that is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen.

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out

what is changed in the "Remarks" portion of the amendment.

Claim 177 has not been amended in the present amendment. All of claims 210-213 are previously presented new claims in the sense that they were not present in the patent as issued and are being amended by the present amendment. So that the examiner can see how the claims are being amended from the previous version of these claims, the following is a recitation of all of these claims shown in the conventional amended format:

210 (Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid,

wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid.

211 (Amended). The therapeutic composition of claim 210, wherein said genetically-engineered antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, and said genetically-engineered antibody of (2)(a) is obtained from DNA encoding a monoclonal antibody that inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid and said monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of human beta-amyloid.

212 (Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid,

wherein said human monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen.

213 (Amended). The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

Claims 210-211 have been rejected under 35 U.S.C. 102(a) as being anticipated by Bickel, as further evidenced by Solomon (2002). The examiner acknowledges that Bickel's AMY-33 antibody is a mouse monoclonal. The examiner is of the opinion that the claim language still encompasses this antibody as the examiner considers that it is a genetically engineered monoclonal antibody, and as the examiner considers that the claim language includes molecules comprising an

antigen binding fragment thereof. The examiner states that as substantially amended, the claims are now clearly on point that the monoclonal of the dependent claims applies as a genetically engineered antibody not limited, for example, to antibodies of chimeric or humanized form.

Claims 210 and 211 have also been rejected under 35 U.S.C. 102(b) as being anticipated by Stern, as further evidenced by Solomon (2002). As with the Bickel reference, the examiner states that Stern anticipates as it is a genetically engineered monoclonal antibody and comprises an antigen binding fragment thereof.

As to applicant's argument that the term "genetically engineered antibody" does not read on monoclonals, the examiner states that the terms are not defined in any way within the claims and neither Haber nor the present specification at column 10, lines 1-3, serve to provide any definition or structural constraint to the antibodies that preclude the murine monoclonal from the genetically engineered antibody of claims 210 and 211. The examiner states that the process of making monoclonals includes the genetic manipulation of DNA and cells, notably cell fusion techniques. Accordingly, the examiner states that monoclonals are not inconsistent with genetic engineering. The examiner states that applicants appear to be construing

their claims to be directed to procedures regarding the making of chimeric or humanized antibodies, but no limitations direct to structures of chimeric or humanized form. This rejection is respectfully traversed.

It is respectfully submitted that claims 210 and 211 do, indeed, recite specific structure that is not possessed by the antibodies of Bickel or Stern, which structure has not been acknowledged or discussed by the examiner. Claim 210 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and either a genetically engineered antibody or a fragment of the genetically engineered antibody. The antibodies are further defined as requiring that they be able to inhibit aggregation of beta-amyloid or maintain the solubility of soluble beta-amyloid. However, the claim continues in the last seven lines to specify, "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that …." The examiner has not explained how AMY-33 can be considered to be a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody.

It may be true in the broad sense of the term "genetic engineering" that monoclonal antibodies can be considered to have been genetically-engineered when they are produced, for example, by hybridoma technology that is genetic

fusion of spleen cells and myeloma cells, which is a form of genetic engineering. However, claim 210 does not read on a standard murine monoclonal antibody that is obtained, for example, by standard hybridoma technology. Claim 210 requires that the genetically engineered antibody be one that is "obtained from DNA encoding a monoclonal antibody." Thus, "genetically-engineered antibody" is distinguished from "monoclonal antibody" by the claim language itself. It must be something different from a monoclonal antibody if it is obtained from DNA encoding a monoclonal antibody. This language cannot be simply read out of the claim.

It is of course well known, for example from the present specification at column 10, lines 1-3, and the Haber reference discussed in applicant's previous response and elsewhere herein, that genetically-engineered antibodies can be obtained by genetically-engineering DNA encoding a monoclonal antibody. Clearly, the claims are directed to the latter type of antibody and not to monoclonal antibodies *per se*. Even if the examiner considers that monoclonal antibodies are "genetically-engineered" in another sense of this term, the claim language quoted above requires that a "genetically-engineered antibody" be something other than a simple "monoclonal antibody" obtained, for example, by standard hybridoma techniques. Claim 210 requires that the

"genetically-engineered antibodies" must be obtained from DNA encoding a monoclonal antibody.

Thus, the phrase "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody" requires that DNA encoding the monoclonal antibody has been genetically-engineered after the monoclonal antibody has been initially produced and selected, for example, by hybridoma technology. DNA encoding the monoclonal antibodies of Bickel and Stern has not been genetically-engineered after initial production and selection and therefore those antibodies cannot be considered to be "obtained from DNA encoding a monoclonal antibody." Engineering of DNA encoding the monoclonal antibody after selection is known, for example from Haber 1992, to be useful in producing humanized antibodies and single chain antibodies. The antibody of Stern and Bickel have not had their DNA altered after initial production and selection and therefore the present claims 210 and 211 do not read on them.

The supporting specification supports this interpretation. Column 10, lines 1-3, reads:

> The present invention uses genetically-engineered antibodies obtained from such selected antibodies ….

See also Haber, "Engineered Antibodies as Pharmacological Tools", *Immunological Reviews*, 130:189-212 (1992), which is of

record in this case and has been cited in the present specification at col. 2, lines 59-63, col. 6, lines 7-15, and col. 16, lines 27-33. At column 2 it is cited expressly for support for "engineered" antibodies and at column 6 it is cited expressly for preparing the antibody that can be used. Thus, techniques for forming genetically-engineered antibodies from DNA encoding the initially produced and selected monoclonal antibodies were well known as of the effective filing date of this application, as is evidenced by the present specification.

While the antibody of Stern and Bickel could be considered to be broadly interpreted as being "such selected antibodies" (as this term is used at the above-quoted column 10, lines 1-3), they cannot be interpreted as being genetically-engineered antibodies obtained from DNA encoding such selected antibodies. When this claim language is given appropriate weight, it must be understood that antibodies of Stern and Bickel do not fall within the scope of either claim 210 or 211 and thus do not anticipate these claims.

As to the examiner's statement that antibodies of Stern and Bickel comprise fragments of a genetically-engineered antibody, it is first pointed out that if the antibodies are not a genetically-engineered antibody obtained from DNA encoding a monoclonal antibody, they can contain no

fragment of such a genetically-engineered antibody. Furthermore, the present claims do not read on molecules that "comprise a fragment." The claims read on either the genetically-engineered antibody or a fragment thereof. There is no "comprising" language in the claim for that particular molecule. The "comprising" language is only for the composition in that one must have the antibody and the carrier and one can add other things to the carrier. However, this language does not say that the molecule that is the antibody comprises a fragment. Accordingly, as the claims do not read on molecules comprising a fragment of the genetically-engineered antibody and, in any event, as the antibody of Stern and Bickel is not a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody, the Stern and Bickel antibody does not anticipate either of claims 210 or 211. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It should be noted that new process claim 214 cannot be considered to be anticipated by any of the references of record as it requires selection of the monoclonal antibody first, followed by genetic engineering of the DNA of the selected antibody. This does not occur with the references of record, as explained with respect to the composition claims. Claim 214 is the inherent method of making the composition of

claim 210 and is therefore directed to the same invention as that of claim 210. It is not independent and distinct therefrom.

Claims 210 to 213 have been rejected under 35 U.S.C. 102(b) as anticipated by Gaskin as evidenced by Solomon 2002. The examiner states that Gaskin teaches four human monoclonal antibodies that bind epitope 1-28 of human A-beta and therefore also would be suitably obtained thereby. Thus, the examiner considers the antibodies of Gaskin to meet the structural limitations of the claims. The examiner notes applicant's argument that Gaskin could not possibly have been obtained using A-beta 1-28 as an immunogen as Gaskin notes at page 1184 that there is a contribution from the 29-40 region to the reactive epitope and that the epitope differs from those recognized by xenogeneic antibodies raised against A-beta 1-28. However, the examiner states that that they are not persuasive. The examiner notes that the claims are recited in alternative form and that, while the claims stipulate that the antibody is obtainable using residues 1-28 of human beta amyloid as an immunogen, this limitation is not required. The examiner states that the statement is followed by the alternative "or recognizes an epitope within 1-28 of beta-amyloid." The examiner further states that the "obtainable" limitation is a product-by-process limitation and

the claim is directed to a composition or product. The examiner further states that "genetically engineered" is a product-by-process limitation and that no distinguishing structure is conveyed. The examiner states that no evidence supports the conclusion that the Gaskin antibodies cannot be obtained using residues 1-28 of beta-amyloid as an immunogen. The examiner states the immunization with full length beta-amyloid does in effect "use" A-beta 1-28 as this is interpreted as open language. The examiner states that the claims are not limited to immunization with a peptide consisting of residues 1-28. The examiner states that as the antibodies of Gaskin are monoclonal antibodies, they also meet the claim limitation to genetic-engineered antibodies for the reasons discussed above with respect to the rejections over Stern and Bickel. This rejection is respectfully traversed.

First of all, with respect to claims 210 and 211, the human monoclonal antibodies of Gaskin are not "genetically-engineered antibodies" in accordance with the language of claims 210 and 211 in view of the requirement that such a genetically engineered antibody be obtained from DNA encoding a monoclonal antibody. Accordingly, for the same reasons as discussed hereinabove with respect to the rejections over Stern and Bickel, Gaskin does not anticipate the genetically-engineered antibody of claims 210 and 211.

The examiner states in the second full paragraph on page 12 that the claims use alternative form, i.e., obtainable using residues 1-28 or recognizing an epitope within residues 1-28. However, only claims 210 and 211 contain such alternative language. This argument does not apply to claims 212 and 213, which require that the antibody be obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

As to the examiner's statement that the term "using" is interpreted as open language such that the claim is broad enough to read on immunization with 1-43, the claims have now been amended to specify that the human monoclonal antibody is obtainable using "a peptide consisting of residues 1-28 of beta-amyloid as an immunogen." This certainly does not encompass any antibody that could not have been raised using a peptide consisting of resides 1-28, as is the case with Gaskin. The language of Gaskin makes clear on its face that the antibody could not have been obtained using a peptide consisting of residues 1-28. As Gaskin notes, at page 1184, there is a contribution from the 29-40 region to the reactive epitope. Accordingly, there is a structural difference between antibodies that are obtainable using a peptide consisting of residues 1-28 and the antibodies of Gaskin. Whether the present claim language is considered to be

"product by process" or not, the process necessitates a product having a certain structure, which is not present in Gaskin's antibodies. Applicant is not arguing that there is no anticipation because the processes of producing the antibodies are different. It is applicant's position that there is no anticipation because the antibodies themselves are different, as explained above. Accordingly, for all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 210 and 211 have been rejected under 35 U.S.C. 102(a) as being anticipated by Walker as evidenced by Solomon (2002). The examiner states that Walker teaches a murine monoclonal antibody 10D5 specific for residues 1-16 of A-beta. The examiner considers that 10D5 anticipates the present claims because all monoclonal antibodies are genetically engineered. In other words, the examiner considers this rejection to be applicable for the same reasons as discussed above with respect to the rejection of claims 210 and 211 over Stern, Bickel and Gaskin. This rejection is respectfully traversed.

As discussed above, the present claims do not read on monoclonal antibodies directly obtained using, for example, standard hybridoma technology obtained by fusing spleen cells

and myeloma cells. The present claims require that the genetically-engineered antibodies be obtained from DNA encoding such monoclonal antibodies. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above for Stern and Bickel are respectfully urged.

Claims 210-213 and 177 have been rejected under 35 U.S.C. 102(e) as being anticipated by Anderson as evidenced by Solomon (2002). The examiner states that Anderson teaches administration of antibodies that bind to beta-amyloid, particularly beta-amyloid residues 1-28, for the treatment and prevention of vascular hemorrhaging in Alzheimer's disease. The examiner states that the antibodies of Anderson are characterized as being obtainable using A-beta 1-28 antigen, and include antibodies that are modified to become human, i.e., chimeric or humanized forms generated by recombinant genetic engineering and that the antibodies may be of single chain form. The examiner points out that the antibodies of Anderson are included in pharmaceutical compositions and are provided with a pharmaceutically acceptable carrier. This rejection is respectfully traversed.

First, it is noted that the effective date of the Anderson patent as a reference is November 22, 1994, when it was filed. This date is less than a month prior to the

application date applicable to the present application, December 16, 1994. The present invention was conceived prior to November 22, 1994, and that conception was communicated to the United States prior to November 22, 1994. Furthermore, this conception was linked by reasonable diligence of the patent attorneys preparing the application from a date immediately prior to November 22, 1994, through to the constructive reduction to practice on December 16, 1994.

As proof of these facts, attached hereto is a declaration under 37 C.F.R. 1.131 of the present inventor, Dr. Beka Solomon, supported by factual declarations of Kenneth I. Kohn, Shulamit Hirsch, and Roger L. Browdy, and 26 documentary exhibits (Exhibits A-Z). The facts show that documents Exhibits K and O were in the United States prior to November 22, 2006, and that the combination of these disclosures in the United States establishes conception of the presently claimed invention. The declarations of Kohn, Hirsch, and Browdy set forth the factual foundation establishing reasonable diligence from a date immediately prior to November 22, 1994, and the filing date of December 6, 1994.

The conclusion that can be drawn from all of this evidence is that Mr. Kohn, in the United States, received Dr. Solomon's comments on the first draft of the application within two or three days of Monday, November 14, 1994, when it

was sent to him by DHL courier (Exhibit F). Furthermore, on Wednesday, November 16, 1994, Mr. Kohn received Dr. Solomon's *Nature* manuscript to review, which was directly related to the subject matter of the application (Exhibits G, N and O). It is apparent that Mr. Kohn's office worked on this application between those dates and December 2, 1994, when another draft was sent to Ramot (Exhibit P). They also worked on preparing the formal papers (Exhibits Q and R).

On December 7, 1994, Mr. Kohn's office received by fax additional remarks and changes from Dr. Solomon (Exhibit S). They subsequently worked on further revisions of the draft application, as is evidenced by Exhibits W and X, until the application was filed on December 16, 1994.

Accordingly, it is apparent that there was reasonable diligence in the United States toward constructive reduction to practice from November 22, 1994, through December 16, 1994. Thus, Anderson is not available as a reference. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Even if Anderson were available as a reference with respect to the present application, it does not anticipate. None of the antibodies of Anderson can anticipate any of the present claims because Anderson does not teach any specific antibodies. Anderson may present a wish to know if certain

antibodies may exist, but it certainly does not present an enabling disclosure for any antibody that satisfies his requirements. While a U.S. patent is presumed enabling for the claimed subject matter, the subject matter being relied on by the examiner is not claimed in Anderson, and thus there is no presumption that the disclosure with respect to the antibodies is enabling.

It is not entirely clear from a reading of Anderson exactly what are the properties of the antibodies that he wishes for. At column 4, lines 34-36, the invention appears to relate to agents such as monoclonal antibodies that prevent the amyloid peptide from interacting with a thrombolytic agent, such as tPA. At column 4, lines 45-50, Anderson states that the antibody binds beta-amyloid peptide, but does not block the ability of fibrin to bind and stimulate the thrombolytic agent. Thus, it is apparent that the antibody is supposed to bind the amyloid peptide at the binding site of the thrombolytic agent to the amyloid peptide and yet not block the thrombolytic agent's ability to bind to fibrin. However, at column 6, lines 61-65, Anderson talks about anti-amyloid antibodies that can prevent or inhibit thrombin-amyloid peptide association. At column 9, lines 9-13, Anderson states that preferred binding agents are obtained by screening among antibodies elicited in response to

immunization with a beta-amyloid peptide. However, it does not state with what it is being screened.

While Anderson states at column 9, lines 30-40, that preferred biologically active fragments of A-beta peptide lack amino acid residues 29-42, there is no suggestion that all antibodies raised against an A-beta 1-28 fraction will bind to A-beta in such a manner as to prevent binding by either thrombin or a thrombolytic agent, such as tPA. In the paragraph bridging columns 11 and 12, Anderson states that, in a highly preferred embodiment, monoclonal antibodies are screened to remove those antibodies that are additionally capable of specifically binding to fibrin.

Nowhere in Anderson is it suggested what epitope of A-beta is the binding epitope for either thrombin or tPA. Certainly one of ordinary skill in the art reading Anderson would not expect that all antibodies raised against A-beta 1-28 might have these very special properties. Solomon (2002) does not teach that all antibodies raised against A-beta 1-28 will have the properties required by the present claims, i.e., the inhibition of aggregation of beta-amyloid or the maintenance of the solubility of soluble beta-amyloid. Thus, there is no certainty that any antibody found to have Anderson's desired properties will necessarily have the properties required by the present claims. Anderson's

disclosure with respect to antibodies is entirely prophetic and very short on facts. The claims do not relate to antibodies, apparently confirming that there is no enabling disclosure in Anderson for that part of the disclosed invention. Accordingly, it is not understood on what basis the examiner contends that Anderson anticipates the present claims.

Anderson does not make any antibody whatsoever in the examples. Thus, it is not possible to test any antibody of Anderson for aggregation inhibition. If it is the examiner's position that an antibody in accordance with Anderson might have the properties required for the antibodies of the present invention, this position is insufficient to establish anticipation in light of cases such as *Ex parte Cyba*, 155 USPQ 756, 757 (PTO Bd App 1967), which states:

> In order that a rejection based upon inherency may be sustained, such inherency must be certain.

See also *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981), quoting with approval from *Hansgirg v. Kemmer*, 40 USPQ 665, 667 (CCPA 1939):

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

See also *Ex parte Skinner*, 1 USPQ2d 1788, 1788-1789 (BPAI 1986), where it states:

> It is by now well established that the burden of establishing a *prima facie* case of anticipation resides with the Patent and Trademark Office. ... We are mindful that there is a line of cases represented by *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971) which indicates that where an examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the examiner possesses the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. Nevertheless, before an applicant can be put to this burdensome task, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art. [Emphasis added]

Accordingly, Anderson discloses no specific antibody nor does Anderson disclose an epitope on A-beta to which such an antibody should be directed. Accordingly, there is no reason to believe that each and every antibody having the properties wished for by Anderson will necessarily have the properties presently claimed. This is insufficient evidence on which to establish a *prima facie* case of anticipation. Accordingly, regardless of whether or not Anderson is

available as a reference, reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 210-211 have been rejected under 35 U.S.C. 102(e) as anticipated by Suzuki as evidenced by Solomon 2002. The examiner states that Suzuki teaches a mouse hybridoma producing murine monoclonal antibodies that bind specific portions of beta-amyloid, particularly N-terminal 1-16. The examiner considers that this reference anticipates because a monoclonal antibody is necessarily genetically engineered. This rejection is respectfully traversed.

Suzuki does not anticipate for the same reasons as discussed above for Stern, Bickel and Walker. Claims 210 and 211 do not comprehend monoclonal antibodies, such as those of Suzuki, whose DNA has not been genetically engineered after production by, for example, hybridoma technology. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above for Stern and Bickel are respectfully urged.

Claims 212-213 and 177 have been rejected under 35 U.S.C. 103(a) as obvious over either Bickel or Stern in view of Becker and Anderson. The examiner states that Bickel and Stern teach antibody AMY-33, which is not a human monoclonal antibody. The examiner states that Becker teaches pharmaceutical formulations containing antibodies having

specificity for beta-amyloid peptide for reduction of hyper-immunogenicity *in vivo*, for example, when used to treat or detect amyloid plaques. The examiner states that Anderson also teaches administration of A-beta antibodies of human, humanized, or single chain monoclonal form for treatment of vascular hemorrhaging in Alzheimer's disease and for diagnosis and labeling of amyloid plaque *in vivo*. Thus, the examiner states that the artisan would be motivated by Becker and Anderson to modify the Bickel or Stern antibody with the requisite epitope specificity, to human, humanized, or single chain form for *in vivo* administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson with reduced hyperimmunogenicity *in vivo*. The examiner states that the preferred epitope specificity is provided by the AMY-33 species. This rejection is respectfully traversed.

This is the first rejection under 35 U.S.C. 103 in this Office action. All of the preceding rejections have been anticipation rejections under 35 U.S.C. 102. As opposed to an anticipation rejection, 35 U.S.C. 103 requires that the examiner establish that the invention <u>as a whole</u> was obvious to one of ordinary skill in the art at the time the invention was made. The present invention as a whole includes the novel and unexpected property of preventing beta-amyloid aggregation

or maintaining the solubility of soluble beta-amyloid. This important claimed feature of the present invention is part of the present invention as a whole and would not have been obvious to one of ordinary skill in the art reading Bickel, Stern, Becker, and Anderson (even assuming that Anderson is available as a reference, and it is not as it has been antedated for the reasons discussed above). Bickel and Stern do not suggest that the antibody thereof will inhibit aggregation of beta-amyloid or maintain the solubility of soluble beta-amyloid.

Becker has nothing to do with inhibiting aggregation of beta-amyloid or maintaining solubility of beta-amyloid. It is a paper patent based on no evidence and no experimental results and stating that beta-amyloid that has assumed a predominantly beta sheet conformation is more neurotoxic *in vitro* than beta-amyloid that is predominantly in random coil or alpha-helix configuration (see column 5, lines 27-33). Becker discloses the desirability, at least for diagnostic purposes, of finding conformationally specific antibodies that show a high level of specificity for the beta-amyloid peptide in a specific conformation, while showing markedly less specificity for the same peptide having a different secondary structure (see column 6, lines 22-30).

The question here is what motivation one of ordinary skill in the art would have to use AMY-33 as the antibody of Becker. The examiner has not addressed this issue in the rejection. There is absolutely no reason to believe that AMY-33 would have the very special properties required by Becker for antibodies that can be used in his process. Even if it would have been obvious to try every possible antibody against beta-amyloid in the process of Becker, there would not have been any reasonable expectation that any of those antibodies tried would actually have the very special properties desired by Becker. As there is no motivation to combine Stern and Bickel with Becker, with a reasonable expectation of success, this part of the rejection must be withdrawn.

As to Anderson, Anderson also requires very special properties for the antibody used therein. It must prevent the binding of thrombin or tPA to beta-amyloid. Again, there is absolutely no reasonable expectation that the AMY-33 antibody of Bickel and Stern will prevent the binding of thrombin or tPA to beta-amyloid as required by Anderson. Even if it were obvious to try every possible antibody against beta-amyloid to see if it prevents such binding, there would have been no reasonable expectation of success for AMY-33. The fact that Anderson mentions 1-28 and AMY-33 is raised against 1-28 does not provide the requisite expectation that AMY-33 will prevent

binding of thrombin or tPA to A-beta. There are many epitopes in the 1-28 region. Becker gives no clue where thrombin or tPA may bind to A-beta. Thus, there would be no reasonable expectation that AMY-33 will prevent thrombin or tPA binding.

Accordingly, there is no motivation to combine the references cited by the examiner for any reason, let alone the presently claimed reason to inhibit aggregation of beta-amyloid or maintain its solubility. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

Claim 177 has been rejected under 35 U.S.C. 103(a) as being obvious over Gaskin in view of Becker and Anderson. The examiner states that Gaskin teaches a human monoclonal antibody and composition of the requisite epitope specificity, but which is not a single chain. The examiner states that Becker and Anderson teach administration of antibodies including single chain antibodies. Accordingly, the examiner states that the artisan would be motivated by Becker and Anderson to modify the Gaskin antibody with the requisite epitope specificity to single chain form for *in vivo* administration, detection, and diagnosis of disease or for treatment as taught by either Becker or Anderson. This rejection is respectfully traversed.

As with the antibodies of Bickel and Stern discussed above with respect to the previous obviousness rejection, Gaskin does not disclose that its antibody will inhibit aggregation of beta-amyloid or maintain its solubility, nor does Gaskin suggest that its antibodies will have the conformationally specific properties wished for by Becker or will prevent the binding of thrombin to A-beta, as is required by Anderson. If there is no motivation to use the antibodies of Gaskin therapeutically, there certainly would be no motivation to change their form to that of a single chain antibody, as it would not be obvious to administer the antibodies of Gaskin in any form for *in vivo* administration, detection, and diagnosis of disease or for treatment as taught by either Becker or Anderson. The examiner has not established a *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 212, 213 and 177 have been rejected under 35 U.S.C. 103(a) as obvious over Walker in view of Becker and Anderson. The examiner considers that the artisan would have been motivated by Becker and Anderson to modify the Walker antibody with the requisite epitope specificity to human, humanized or single chain form for *in vivo* administration, detection, and diagnosis of disease or for treatment as taught

by either Becker or Anderson. This rejection is respectfully traversed.

This rejection must fall for the same reasons as discussed above with respect to the other obviousness rejections. There would have been no reasonable expectation of success that the 10D5 antibody of Walker would have the very special properties required by Becker or Anderson for therapeutic or diagnostic use. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above with respect to those rejections using Bickel, Stern, or Gaskin as the primary references are respectfully urged.

Claims 212-213 and 177 have been rejected under 35 U.S.C. 103(a) as obvious over Suzuki in view of Becker and Anderson. The examiner's reasoning is the same as discussed above with respect to Walker, Stern, and Bickel. This rejection is respectfully traversed.

As with the previous obviousness rejections there is absolutely nothing in Suzuki that would create a reasonable expectation that it could successfully be used for any of the purposes required by Becker and Anderson for their antibodies. Accordingly, this rejection must be withdrawn for the same reasons as discussed above with respect to the other obviousness rejections.

Attached hereto is an Information Disclosure Statement calling the examiner's attention to divisional application no 11/358,951 and the rejections made in the prosecution history thereof, as well as the references cited therein.

The examiner's attention is drawn to the fact that a new declaration has been filed in the file of the patent underlying this reissue, patent no. 5,688,651. It has now been discovered that there was an informality in the original declaration filed in that case as the specification had been further revised after that declaration had been executed. To correct this problem, a substitute declaration has now been executed and filed in the patent file. This procedure is akin to the procedure set forth in MPEP 603.01 about filing a supplemental declaration after an application is allowed. These supplemental declarations are just placed in the file and no receipt or acknowledgment is sent to the applicant. The undersigned has been informed by the Office of Patent Legal Administration that supplemental declarations filed after the issuance of a patent are treated in the same way and there is no necessity of making this correction in the course of a reissue proceeding.

It is submitted that all the claims now present in the case clearly define over the references of record and

fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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